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Two Pairs of Male Monozygotic Twins Discordant for Wiedemann-Beckwith Syndrome

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Wiedemann-Beckwith syndrome (WBS) is a congenital anomaly syndrome which classically consists of exomphalos, macroglossia, and gigantism. The syndrome is also associated with a variety of minor anomalies and affected individuals have an increased risk of developing rare embryonal cell tumors. To date, 15 monozygotic (MZ) twin pairs have been reported of which 13 are discordant for WBS. All except one pair of the discordant WBS twin pairs have been female. We report two pairs of male MZ twins, each discordant for WBS. © 1996 Wiley-Liss, Inc.

KEY WORDS: Wiedemann-Beckwith syndrome, discordant monozygotic twins, male monozygotic twins, imprinting, twinning

INTRODUCTION

The Wiedemann-Beckwith syndrome (WBS) consists of exomphalos, macroglossia, and gigantism (EMG syndrome). Other anomalies include ear pits/creases, visceromegaly, hemihypertrophy, neonatal hypoglycemia, facial nevus flammeus, and a predisposition to malignancies such as Wilms tumor (nephroblastoma), adrenocortical carcinoma, hepatoblastoma, rhabdomyosarcoma, and, occasionally, pancreatic tumors and neuroblastoma [Wiedemann, 1964; Beckwith, 1969]. Fifteen monozygotic (MZ) twin pairs with WBS have been reported to date. Of these pairs 12 are female and discordant for WBS [Benke, 1978; Berry et al., 1980; Bose et al., 1985; Clayton-Smith et al., 1992; Estabrooks et al., 1989; Franceschini et al., 1993; Litz et al., 1988; Lubinsky et al., 1974; Olney et al., 1988]. There is 1 female twin pair concordant for WBS but with varying clinical phenotype and one male pair concordant for WBS [Clayton-Smith et al., 1992]. The last pair are male monozygotic twins that are discordant for WBS [Chien et al., 1990]. The majority of discordant WBS twins have been female with only a single reported case of male twins discordant for WBS. We present clinical information on two male monozygotic twins that are discordant for WBS.

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CLINICAL REPORTS

Pair 1

Monozygotic twin male infants were born to a 36-year-old G3P1SA1 caucasian woman. The family history was unremarkable except for male dizygotic twins on the paternal side and female dizygotic twins on the maternal side.

The pregnancy was uncomplicated except for occasional spotting in the first trimester. Labor was spontaneous with breech position necessitating a cesarean section at 37 weeks gestation by dates. Examination of the twins at birth suggested an estimated gestational age of 34 weeks.

The affected twin had Apgar scores of 6 at 1 minute and 8 at 5 minutes. His birth weight was 3,000 g (>90th centile for 34 weeks), length 50 cm (>90th centile), and head circumference (OFC) 31.7 cm (50–75th centile). At birth he was noted to have mild transient hypoglycemia necessitating intravenous dextrose. He was found to have an omphalocele, visceromegaly, macroglossia, and bilateral ear creases with indentations on the posterior helix. He had a nevus flammeus over the eyelids, nose, and nasal bridge. There was no evidence of asymmetry. Cardiac examination documented a functional systolic murmur. He had bilateral inguinal hernias and undescended testes repaired at age 1 month. He was jaundiced at age 2 days requiring no treatment and had a single seizure at age 12 weeks.

Twin B shared none of the abnormalities of his brother. His birth weight was 2,200 g (50th centile for 34 weeks), length 45 cm (75th centile), and head circumference (OFC) 30.2 cm (25th centile). Apgar scores were 6 at 1 minute and 6 at 5 minutes. He had tran-

sient hypoglycemia treated with dextrose. He was jaundiced at 3–4 days of age which necessitated phototherapy. He had no evidence of visceromegaly, macroglossia, nor ear creases.

The twins had no evidence of developmental delay to the age of 4 years. Twin A continued to have growth in height and weight well above the 95th centile. At age 4 years twin A weighed 20.6 kg (>95th centile), was 109.5 cm tall (>95th centile), and had an OFC of 49.5 cm (40th centile). He continued to show no evidence of asymmetry but had persistent visceromegaly of the liver and spleen. Frequent abdominal ultrasound and AFP values were normal. Twin B at 4 years of age weighed 16.5 kg (50th centile), was 103.5 cm tall (50th centile), and had an OFC of 49 cm (25th centile).

Pair 2

Monozygotic male twins were born at term to a 38-year-old G3P2 oriental mother. There was no family history of twinning or malformations.

Omphalocele of one of the twins was diagnosed by obstetric ultrasound. Delivery was by elective cesarean section for placenta previa. The affected twin (twin A, Figs. 1, 2) had Apgar scores of 3 at 1 minute, 5 at 5 minutes, and 7 at 10 minutes. Birth weight was 3,685 g (>90th centile). He had an omphalocele, macroglossia, cleft of the soft palate, frontal nevus flammeus, cryptorchidism with bilateral inguinal hernias, and bilateral ear lobe creases. He had poor cardiac function, with an ASD, PDA, mitral, and tricuspid valve regurgitation. He had persistent hypoglycemia and tolerated feeds poorly. The omphalocele healed spontaneously without surgical management. He was found to have bilateral optic nerve dysfunction, with cerebral cortical atrophy of unknown cause and questionable seizure activity. Physical and social development were delayed and at the age of 10 months, he weighed less than his brother.

Due to the risk of embryonal tumors seen in WBS he was followed every 3 months with abdominal ultrasound and AFP. At age 12 months he was noted to have a mass developing in the liver. Pathology of the tumor, following surgical resection, showed a hepatoblastoma with well differentiated epithelial patterns. He is currently receiving chemotherapy of cis-platinum, vincristine, and 5-fluorouracil.

Twin B (Figs. 1, 3) weighed 2,950 g (25th centile) at birth, and there were no postnatal problems or signs of WBS. Development has been normal.

INVESTIGATIONS

High resolution chromosome analysis on peripheral lymphocytes showed normal chromosomes in both twin pairs with no evidence of deletions, duplications, or rearrangements of chromosome 11. Microscopic sections of the placenta and fetal membranes of pair 1 documented monochorionic/diamniotic sacs confirming that the twins are MZ. Pair 2 had fused, dichorionic placentas. Molecular zygosity testing on peripheral lymphocytes identified both pairs as being MZ. Probes used for each of the twin pairs included HMF1, 3′HVR, and YNH24 [Buroker et al., 1987; Higgs et al., 1986; Nakamura et al., 1987]. These probes establish that the twins are likely monozygous with 99.99% certainty.

Molecular testing was also undertaken using 11p15 probes (Table I) to search for 11p15 uniparental disomy, which has been reported previously in some cases of WBS [Grundy et al., 1991]. These results exclude maternal disomy and paternal isodisomy in pair 1 at all 3 loci, including IGF2 which is a candidate gene for WBS, but do not exclude paternal heterodisomy at any of the loci. Paternal disomy is excluded in pair 2 at both loci tested, but maternal heterodisomy is not excluded at the insulin locus. Since all 4 twins were heterozygous at all loci tested, there was no evidence of deletion of alleles. In pair 2, the relative density of the HRAS alleles by densitometric analysis of the autoradiogram showed the ratio of allele 1 versus 2 to be 1.04 for twin A and 1.03 for twin B showing that neither allele was duplicated.

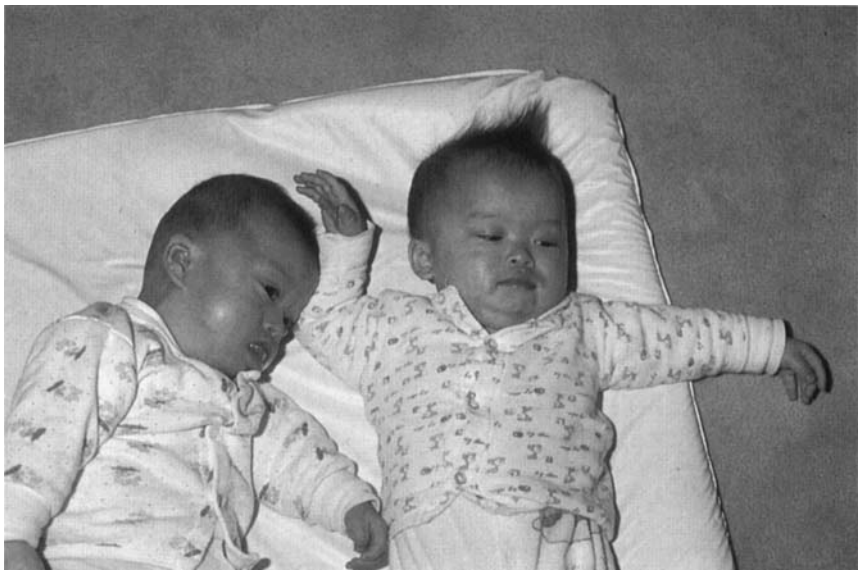


Fig. 1. Pair 2. The twins at age 10 months. Twin A **(right)** shows macroglossia.

Fig. 2. Pair 2. Twin A, showing ear creases.

TABLE I. Genotypes of the Twin Pairs and Their Parents at Chromosome 11p15 Loci*

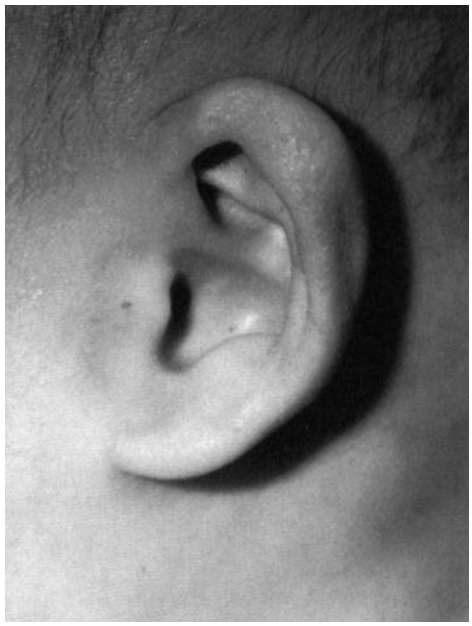
Pair 1						
Probe		TH		INS		IGFII
Mother	1,1		1,3		1,1	
Father		1,3		2,3		1,2
Twin A	1,3		2,3		1,2	
Twin B	1,3		2,3		1,2	
Pair 2						
Probe		HRAS		INS		
Mother	1,1		1,2			
Father		2,2		1,1		
Twin A	1,2		1,2			
Twin B	1,2		1,2			

*TH is a tetranucleotide repeat PCR-based polymorphism. INS is a VNTR polymorphism assay by Southern blot. IGFII, a candidate gene for BWS, is a PCR-based RFLP. RFLP fragments and PCR products were numbered 1 to 3, within each family, according to decreasing length. HRAS is a VNTR polymorphism, assayed by Southern blot, distal to probes 1–3.

Studies have been reported that show that monozygotic twins often share blood supplies, resulting in similar chromosomal or molecular results on analysis of samples obtained from blood. Even with complete admixture of the two blood samples, however, paternal disomy should have been evident if present. Parallel tissue samples would be helpful in ensuring that chromosomes/DNA obtained are distinct for each of the twins. Such tissue samples could not be obtained for these twin pairs at this time.

DISCUSSION

Wiedemann-Beckwith syndrome is a congenital anomaly syndrome which consists of exomphalos, macroglossia, and gigantism in association with a variety of minor anomalies and an increased risk of developing rare embryonal cell tumors. WBS most frequently occurs as a sporadic disorder [Junien, 1992]. Cytogenetic analysis has shown that some cases of WBS were associated with duplication of paternal material on chromosome 11p [Brown et al., 1990; Kubota et al., 1994]. WBS cases associated with chromosomal rearrangements and breakpoints in 11p15 have all been maternal in origin [Mannens et al., 1991; Norman et al., 1992; Waziri et al., 1983]. Autosomal dominant inheritance is also well recognized in WBS [Montou et al., 1992; Niikawa et al., 1986]; however, there is an unusual pattern of transmission with a 3-fold excess of female carriers. These inheritance patterns suggest that sex-specific imprinting may play an important role in WBS [Brown et al., 1990; Hoovers et al., 1992; Lubinsky and Hall, 1991; Montou et al., 1992].



A number of sporadic WBS cases which exhibit paternal UPD (uniparental isodisomy) of the 11p15 loci further implicate imprinting in the WBS phenotype [Grundy et al., 1991; Henry et al., 1991, 1993; Nystrom et al., 1992; Weksberg et al., 1993b]. Uniparental heterodisomy has not yet been identified as a cause of WBS but may at some point prove to be an additional cause of WBS with lack of maternal contribution. It has been suggested that there is an increased risk for malignancy in those WBS cases shown to have UPD [Henry et al., 1993].

Insulin-like growth factor II (IGF2) is a mitogenic peptide which has been mapped to 11p15 [Bell et al., 1985]. Recently, IGF2 has been found to be parentally imprinted in tissues from normal and from WBS individuals, with the paternal allele being exclusively expressed during embryogenesis while the maternal allele is inactive [Ohlsson et al., 1993; Rainier et al., 1993]. Relaxation of the IGF2 imprint has also been reported in Wilms tumors, with resultant expression of both parental alleles in the tumor tissue [Ogawa et al., 1993; Rainier et al., 1993]. Fibroblasts from four of six WBS

individuals have shown biallelic expression of IGF2, supporting the theory that WBS is due to disruption of imprinting, leading to IGF2 overexpression and subsequent overgrowth and development of embryonal tumors [Weksberg et al., 1993a,b].

Of interest in WBS has been the increased number of twin pairs discordant for WBS features. The majority of the cases have been female with only one pair of male monozygotic twins discordant for WBS [Benke, 1978; Berry et al., 1980; Bose et al., 1985; Chien et al., 1990; Clayton-Smith et al., 1992; Estabrooks et al., 1989; Franceschini et al., 1993; Litz et al., 1988; Lunbinsky et al., 1974; Olney et al., 1988]. This case report presents clinical information on an additional two pairs of male monozygotic twins discordant for WBS. Twin A of the first twin pair has features consistent with WBS. Twin A of the second twin pair has numerous features of WBS including omphalocele, macrosomia, macroglossia, frontal nevus flammeus, bilateral ear lobe creases, hypoglycemia, and an embryonal tumor, hepatoblastoma. The cleft palate, cardiac anomaly, optic nerve dysfunction, and cerebral cortical atrophy are not features commonly seen in WBS. Simpson-Golabi-Behmel (SGB) syndrome shares many features with WBS but in addition may have cleft palate and cardiac anomalies as is seen in this twin [Behmel et al., 1984; Garganta and Bodurtha, 1992; Golabi and Rosen, 1984; Gorlin et al., 1990; Hughes-Benzie et al., 1992a; Simpson et al., 1973]. Cerebral cortical atrophy and optic nerve dysfunction are not seen in either condition and are of unknown cause in this child. Additional features commonly seen in SGB syndrome that were not seen in this individual include polydactyly, supernumerary nipples, midline groove of lower lip, and dysplastic fingernails. The lack of these features makes it difficult to establish a diagnosis of SGB in this twin.

Wilms tumor and neuroblastoma have been reported in SGB [Hughes-Benzie et al., 1992b; Xuan et al., 1993]. Our patient developed hepatoblastoma, which is commonly reported in WBS but has yet to be reported in SGB.

SGB is an X-linked condition; therefore one might expect that male monozygotic twins would be concordant for the condition unless a new mutation arose as a post-zygotic event. Female monozygotic twins can be discordant for X-linked conditions due to non-random X-inactivation, which does not occur in males.

Overall, both twin pairs have features consistent with the diagnosis of WBS. There are not enough features in the second twin pair to establish a diagnosis of SGB at the present time.

Monozygotic twins are more commonly seen in WBS than in other syndromes with genomic imprinting [Clayton-Smith et al., 1992]. Monozygotic twinning occurs at 8–10 days gestation, which is around the time of X-inactivation [Boklage, 1981; James, 1980, 1988]. In addition, monozygotic twins are more commonly female [James, 1980; Hall, 1986]. Lubinsky and Hall [1991] noted the association of WBS occurring discordantly in female monozygotic twins and proposed that the process of X-inactivation or the presence of more than one X chromosome may influence imprinting at autosomal loci such as the locus for WBS. The finding of three male monozygotic twins discordant for WBS suggests that X-inactivation or the presence of more than one X chromosome may not have a critical role in monozygotic twinning and/or autosomal imprinting in WBS.

One explanation for the excess of MZ female twins discordant for WBS has been proposed to be due to "contamination by an X-linked condition (SGB) with differing X-inactivation in female twin pairs" [Hughes-Benzie et al., 1992a]. In WBS, segmental UPD and somatic mosaicism have been demonstrated. This suggests that the UPD arose following a postzygotic event [Henry et al., 1993]. The question then raised is does monozygotic twinning, a post-zygotic event, predispose to alteration of autosomal imprinting or does the altered imprinting result in two different cell lines being present that predispose to monozygotic twinning? Likewise the two events may occur secondary to some other phenomenon. Côté and Gyftodimou [1991] propose that the "postzygotic occurrence (of mitotic crossing-over) before an embryo differentiates into MZ twins is theoretically predicted to have disrupting effects on genomic imprinting and cis-acting sequences, with consequences ranging from early lethality to MZ twin discordance." In such a situation mitotic crossing over can occur in autosomes as well as in X chromosomes. They hypothesize that if mitotic crossing over involves the X chromosome, it may lead to abnormal inactivation thus resulting in female MZ twins discordant for X linked conditions. Crossing over involving autosomes could result in abnormal imprinting and discordant monozygotic twins.

The three cases of male monozygotic twins discordant for WBS leads one away from the idea of X-inactivation or the presence of more than one X chromosome playing a key role in the development of WBS in monozygotic twins. Neither twin pair showed evidence of paternal isodisomy in close proximity to (Pair 2) or at the WBS candidate gene locus IGF2 (Pair 1). Isodisomy and duplications were only analyzed at a few regions and therefore smaller segments of UPD cannot be excluded.

Evaluation of biallelic expression in these twin pairs would be of interest in the future. This may reveal altered imprinting at the WBS locus resulting in expression from both paternal and maternal alleles. Such altered imprinting in the affected twin would suggest that a possible mitotic crossing over event may have occurred leading to disruption of imprinting.

Further studies looking at monozygotic twins and their imprinted loci may help provide further information on these two interesting developmental processes.

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